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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	ARONHIME *et al.*
Serial No.	:	09/841,025
Filed	:	April 24, 2001
For	:	ZOLPIDEM HEMITARTRATE
Examiner	:	C. Chang
Art Unit	:	1625

Mail Stop AF Amendment
Commissioner for Patents
P.O. Box 1450
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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:
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on
Date: May 25, 2006
Signature: Shawn Huang

Declaration Under 37 C.F.R. § 1.132

I, JUDITH ARONHIME, Ph.D., of Harav Maor Yosef str. 5a, Rehovot 76217, Israel, declare as follows:

I. BACKGROUND

1. I am a named co-inventor of U.S. application Serial No. 09/841,025 ("the '025 application") filed April 24, 2001.

2. I received my Ph.D. and M.Sc. degrees in 1989 and 1983, respectively, from The Hebrew University of Jerusalem, Casali Inst. of Applied Chemistry. Since 1991, I have worked for Teva Pharmaceutical Industries, Ltd. ("Teva"). I am currently Teva's Global Solid State Characterization Manager. In that position, I am responsible for the physical analysis and characterization of drugs developed by Teva API ("Active Pharmaceutical Ingredients"). I am responsible for over 15 analysts in the group.

3. I have reviewed what I understand to be the specification of U.S. patent application Serial No. 09/841,025 and the Office Action mailed March 17, 2006 ("the Office Action").

After the amendment, I see that five claims are pending, claims 161, 162, 261-262, and 280. Claim 161, as amended, reads: "Zolpidem hemitartrate Form D characterized by an X-ray powder diffraction pattern having peaks at about 7.1, 9.5, 14.1, 19.6 and 24.5 ± 0.2 degrees two-theta, and the corresponding d-spacing values of about 12.5, 9.3, 6.3, 4.53, and 3.63 Å." I will refer to the compound as "zolpidem hemitartrate" and to the solid state as "Form D."

4. I have reviewed U.S. Patent No. 6,281,360 issued on August 28, 2001, to Ettema *et al.*, ("the '360 patent"); and Harry G. Brittain, "Polymorphism in Pharmaceutical Solids," pp. 141-163 and 183-225, (Marcel Dekker Inc, NY 1999) ("the Brittain reference").

II. CRYSTALLINE SAMPLE PREPARATION AND ANALYSIS

5. Under by supervision two lots of zolpidem hemitartrate were prepared: Lot I and Lot II. Each Lot was prepared following the guidelines described in the '025 application. Lot I was prepared by exposing micronized Form A to 100% relative humidity for 10 days. Lot II was prepared by exposing Form C to 100% relative humidity for one day.

6. At my request, a powder x-ray diffraction analysis of a sample of each of Lot I and Lot II was performed. The x-ray diffraction analysis was performed on Scintag X-Ray powder diffractometer model X'TRA using a Cu-tube and a solid state detector. The sample was held by a round standard sample holder with round zero background plate. The scanning parameters for Lot I included a range of 2 to 40 degrees 2θ; continuous scan; and a scan rate of 3 deg./min. The scanning parameters for Lot II included a range of 2 to 40 degrees 2θ; continuous scan; and a scan rate of 5 deg./min. for Lot II.

7. It is my opinion, that in each of Lot I and Lot II the zolpidem hemitartrate crystalline form obtained was zolpidem hemitartrate Form D as described in the '025 application. The PXRD crystal analysis for a sample of Lot I as prepared in paragraph 5 showed that the crystal structure of the zolpidem hemitartrate had PXRD peaks at 7.2, 9.5, 14.1, 19.5, and 24.5 degrees

two-theta, which are characteristic of zolpidem hemitartrate Form D. See Exhibit 1, Figure 1. The PXRD crystal analysis for a sample of Lot II as prepared in paragraph 5 showed that the crystal structure of the zolpidem hemitartrate had PXRD peaks at 7.2, 9.6, 14.3, 19.6, and 24.6 degrees two-theta, which are characteristic of zolpidem hemitartrate Form D. See Exhibit 1, Figure 2.

8. If the solvent water or ethanol is present with the crystalline zolpidem hemitartrate Form D, neither is present as part of the crystalline lattice. Although water or ethanol may exists within the crystalline lattice; in this case, we know that the PXRD pattern is unchanged by their presence. Because the PXRD pattern does not change, the crystalline zolpidem hemitartrate Form D would be considered a clathrate that is characterized by the five (5) PXRD peaks as described above.

9. I understand that Lot III was the preparation of zolpidem hemitartrate Form A, which was prepared as follows: Zolpidem crystals (20 g) and MeOH (180 mL) were charged into one liter model reactor equipped with mechanical stirrer, thermometer, and condenser. The mixture was heated to reflux (65°C) to obtain a clear solution which was cooled to 30 °C by direct cooling. MeOH (50 mL) was distilled from the reactor under reduced pressure (30 °C and 30 mbar). Thereafter, the residue was cooled to 20°C and maintained for 3 hrs at this temperature to obtain a suspension. The suspension was further cooled to 0 °C and maintained for 2 hrs at this temperature where a precipitate formed. The precipitate was collected by filtration and the cake washed with MeOH (8 mL) to yield 18.7 g of wet product that was dried at about 50°C for about 15 hours reduced pressure (40 mbar) to yield 15.2g of dry material (yield 76%).

10. At my request, a powdered x-ray diffraction analysis a sample of Lot III prepared in paragraph 9 above was performed. The x-ray diffraction analysis followed the procedure described in paragraph 6 above using a scan rate of 3 deg./min.

11. It is my opinion, that the crystalline zolpidem hemitartrate obtained in paragraph 9 above is zolpidem hemitartrate Form A as described in the '025 application. The PXRD crystal analysis of the sample prepared in paragraph 9 showed that the crystal structure of the zolpidem hemitartrate prepared had PXRD peaks at 6.6, 9.0, 16.1, 16.7, 24.7, and 27.3 degrees two-theta, which are characteristic of zolpidem hemitartrate Form A as described on page 13 of the '025 application. See Exhibit 1, Figure 3.

III. FORMULATION PREPARATION AND ANALYSIS

12. At my request, a formulation of zolpidem hemitartrate Form D using the sample of Lot I was prepared as follows. Zolpidem hemitartrate Form D (10 mg), lactose monohydrate (47 mg), microcrystalline cellulose (Avicel® PH-102) (40 mg), and povidone (2 mg) were mixed for 15 minutes. Magnesium stearate (1 mg) (previously sieved through 35 micron mesh) was added to the mixture and the mixture was stirred for five minutes. The mixture was pressed into tablets using 0.5 tons of pressure. At my request, a PXRD of the formulation was taken. Figure 4 top portion illustrates the PXRD. See Exhibit 1, Figure 4.

13. I compared the PXRD of the crystalline zolpidem hemitartrate Form D taken before formulation (Figure 4, bottom portion) and the PXRD taken after formulation and compression into a tablet (Figure 4, top portion) by overlapping each figure. The formulation PXRD had the characteristic peaks for zolpidem hemitartrate Form D at 7.2, 9.6, 10.4, 14.2 and 24.6 degrees two-theta, in addition to PXRD peaks caused by the excipients within the formulation. The excipients also have a PXRD peak at 19.6; and therefore, the peak at 10.4 was selected to identify the crystalline zolpidem hemitartrate.

14. Thus, in my opinion, zolpidem hemitartrate Form D is stable to physical manipulation during formulation and tabletting.

IV. HYGROSCOPICITY ANALYSIS

15. The hygroscopicity of zolpidem hemitartrate Form D of Lot II and of zolpidem hemitartrate Form A (Lot III) was performed in accordance with the description found in the European Pharmacopeia 5.02 Chapter 5.11 (January 2005). Exhibit 2.

16. At my request and under my supervision, each sample was tested as follows: a glass weighing vessel (50 mm diameter X 15 mm high) was weighed. A sample was placed on the vessel and weighed again. The vessel was placed in a climatic cabinet set at about 80 percent relative humidity and room temperature. After 24 hours the sample was removed and weighed.

17. Zolpidem hemitartrate Form A increased in mass by 0.02 g corresponding to 0.4% by weight.

18. Zolpidem hemitartrate Form D did not increase in mass. Thus, zolpidem hemitartrate Form D did not absorb water under 80% relative humidity.

19. I declare that all statements made herein are true, and that all statements made herein on information and belief are believed to be true, and that all statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity of any United States Patent that would issued from the '025 application.

Dated: 24.05.06 Signed: _____

Judith Aronhime, Ph.D.